(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number
WO 2004/043903 A1

(51) International Patent Classification[7]: C07C 217/62, 217/64, 323/32, C07D 275/04, 307/86, 333/54, 333/56, A61K 31/381, 31/137, 31/343, 31/425, A61P 25/06, 25/18, 25/24

(21) International Application Number:
PCT/US2003/031513

(22) International Filing Date: 24 October 2003 (24.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/424,176 5 November 2002 (05.11.2002) US

(71) Applicant (*for all designated States except US*): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BOULET, Serge, Louis [CA/US]; 10813 Windemere Boulevard, Fishers, IN 46038 (US). FILLA, Sandra, Ann [US/US]; 1542 Arborwoods Drive, Brownsburg, IN 46112 (US). GALLAGHER, Peter, Thaddeus [GB/GB]; Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire RG21 2XA (GB). HUDZIAK, Kevin, John [US/US], 5944 Magnificent Lane, Indianapolis, IN 46234 (US). JOHANSSON, Anette, Margareta [SE/US]; 6350 Brokenhurst Road, Indianapolis, IN 46220 (US). KARANJAWALA, Rushad, E. [US/US]; 9732 Autumn Way, Zionsville, IN 46077 (US). MASTERS, John, Joseph [US/US]; 12047 Flint Stone Court, Fishers, IN 46038 (US). MATASSA, Victor [GB/DE]; Graffinity Pharmaceuticals, Im Neuenheimer Feld 519, 69120 Heidelberg (DE). MATHES, Brian, Michael [US/US]; 5335 Cotton Bay Drive West, Indianapolis, IN 46254 (US). RATHMELL, Richard, Edmund [GB/GB]; Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire RG21 2XA (GB). WHATTON, Maria, Ann [GB/GB]; Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire RG21 2XA (GB). WOLFE, Chad, Nolan [US/US]; 16096 Tenor Way, Noblesville, IN 46060 (US).

(74) Agents: WELCH, Lawrence, T. et al.; Eli Lilly and Company, P.O. Box 6288, Indianapolis, IN 46206-6288 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

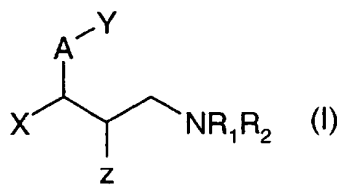
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,*

[Continued on next page]

(54) Title: 3-ARYLOXY/THIO-2, 3-SUBSTITUTED PROPANAMINES AND THEIR USE IN INHIBITING SEROTONIN AND NOREPINEPHRINE REUPTAKE



(I)

(57) Abstract: There is provided a compound of formula (I) wherein A is selected from -O- and -S-; X is selected from phenyl optionally substituted with up to 5 substituents each independently selected from halo, C_1-C_4 alkyl and C_1-C_4 alkoxy, thienyl optionally substituted with up to 3 substituents each independently selected from halo and C_1-C_4 alkyl, and C_2-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl and C_4-C_8 cycloalkylalkyl, each of which may be optionally substituted with up to 3 substituents each independently selected from halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl-S(O)n- where n is 0, 1 or 2, $-CF_3$, -CN and $-CONH_2$; Y is selected from phenyl, naphthyl, dihydrobenzothienyl, benzothiazolyl, benzoisothiazolyl, quinolyl, isoquinolyl, naphthyridyl, thienopyridyl, indanyl, 1,3-benzodioxolyl, benzothienyl, indolyl and benzofuranyl, each of which may be optionally substituted with up to 4 or, where possible, up to 5 substituents each independently selected from halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl-S(O)n- where n is 0, 1 or 2, nitro, acetyl, $-CF_3$, $-SCF_3$ and cyano; and when Y is indolyl it may be substituted or further substituted by an N-substituent selected from C_1-C_4 alkyl; Z is selected from OR_3 or F, wherein R_3 is selected from H, C_1-C_6 alkyl and phenyl C_1-C_6 alkyl; R_1 and R_2 are each independently H or C_1-C_4 alkyl; and pharmaceutically acceptable salts thereofwith the proviso that when Y is optionally substituted phenyl or optionally substituted 1,3-benzodioxolyl and Z is OR_3 and X is optionally substituted phenyl then A is -S-.

WO 2004/043903 A1

MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.